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Cyclic Guanidines. XV.[1] Synthesis and Biological Activities of (Substituted phenyl)-imidazo[1,2-*a*]imidazole Derivatives[2]

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A series of (substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles (**10**) and their 2- or 3-oxo derivatives (**20** and **21**) were unambiguously prepared. These compounds were evaluated for antihypertensive and diuretic activities. Antihypertensive activity in spontaneously hypertensive rats (SHR) was observed in the series of compounds **10**, whereas compounds **20** and **21** did not possess the activity. Diuretic effects in SHR and normotensive rats were observed in both the series of **10** and the 2- or 3-oxo derivatives (**20** and **21**). The relationship between the activities and the substituents on the phenyl ring is discussed.

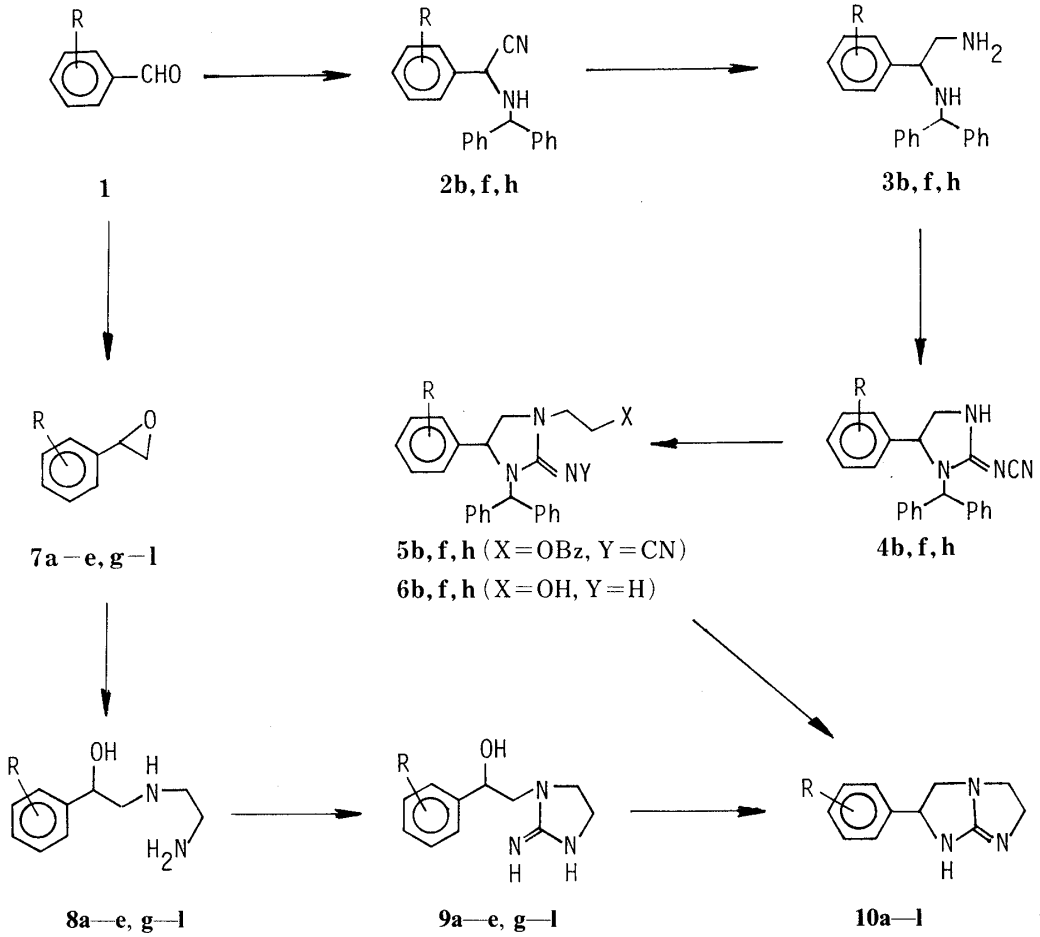
Keywords——bicyclic guanidine; 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole; antihypertensive; diuretic; structure–activity-relationship

We have reported in this series of papers that some cyclic guanidines have potent hypoglycemic[3] and/or platelet aggregation-inhibitory effects.[1] It is also known that some monocyclic guanidines having a phenyl group, for example 2-(2,6-dichlorophenyl)amino-2-imidazoline (clonidine) and 4-(3,4-dichlorophenyl)-2-amino-2-imidazoline (MJ-104592), show potent antihypertensive and diuretic activities.[4] Similarly, phenyl-substituted bicyclic amidines, *e.g.* 6-(2,6-dichlorophenyl)-2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazole[5] (ICI-101187), have potent hypotensive activity. Therefore, it seemed of interest to examine the activities of phenyl-substituted bicyclic guanidine derivatives modified from MJ-104592 and ICI-101187. This paper describes the synthesis and biological activities of (substituted phenyl)-perhydroimidazo[1,2-*a*]imidazoles (**10**) and their 2- or 3-oxo derivatives (**20** and **21**).

Chemistry

Li *et al.*[6] have described the synthesis of 2-phenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (**10a**), mp 168 °C, by cyclization of 2-(2-chloroethyl)imino-4-phenylimidazolidine. In this cyclization, there is a possibility of forming another isomer, 3-phenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole. However, the position of the phenyl group of the compound (**10a**) was not confirmed. On the other hand, the 3-phenyl isomer, mp 167—169 °C (free base) and 227.5—229 °C (hydrochloride), was prepared from 2-(2-chloro-2-phenylethyl)iminoimidazolidine as an antidepressant by Van Gelder *et al.*[7] The compound obtained by Li *et al.* may be the same as the one prepared by Van Gelder *et al.* because of the similar melting points and on the basis of a comparison with the product (**10a**) prepared by the method described below.

The preparation of the target compounds **10** was carried out by two methods. Reaction of the substituted benzaldehydes (**1b**, **f**, **h**) with sodium cyanide in the presence of benzhydrylamine followed by reduction gave 2-benzhydrylamino-2-(substituted phenyl)-ethylamines (**3b**, **f**, **h**) by a method similar to that described by Deitchman *et al.*[4] Heating



R: **a** = H; **b** = 2-Cl; **c** = 3-Cl; **d** = 4-Cl; **e** = 4-Me; **f** = 2-Cl, 4-Cl; **g** = 3-Cl, 4-Cl; **h** = 2-Cl, 6-Cl; **i** = 2-Cl, 6-F; **j** = 2-F, 6-F; **k** = 2-Cl, 6-Me; **l** = 2-Me, 6-Me

Chart 1

of **3** with dimethylcyanoimidodithiocarbamate afforded 2-cyanoimino derivatives (**4b**, **f**, **h**), which reacted with iodoethyl benzoate to give 1-benzoyloxyethyl derivatives (**5b**, **f**, **h**). The cyano and benzhydryl groups of **5** were removed by heating with diluted hydrochloric acid to give 1-(2-hydroxyethyl)-2-imino-4-(substituted phenyl)imidazolidines (**6**), chlorination of which, followed by cyclization afforded the desired products, 2-(substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles (**10b**, **f**, **h**).

Secondly, styrene oxides (**7a—e**, **g—l**) were obtained from the corresponding benzaldehydes (1) by the method of Merz *et al.*[8] Reaction of **7** with excess ethylenediamine predominantly gave a single product, the 2-(2-aminoethyl)amino-1-(substituted phenyl)ethyl alcohols (**8a—e**, **g—l**). The structure of **8** is supported by the proton nuclear magnetic resonance (^{1}H-NMR) spectra which show a much lower chemical shift, at δ 5—6, of the methine proton signal adjacent to the hydroxy group. No signal due to another isomer was observed in the ^{1}H-NMR spectra of the reaction products. Reaction of **9** with cyanogen bromide followed by chlorination and then cyclization easily gave the desired compounds **10a—e**, **g—l**.

2-Phenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (**10a**) obtained here showed mp 115 °C as the free base and 207—209 °C as the hydrochloride. In the ^{1}H-NMR spectrum of the free base of **10a**, the methine proton at the 2-position was observed at δ 5.12 (t) in DMSO-d_6.

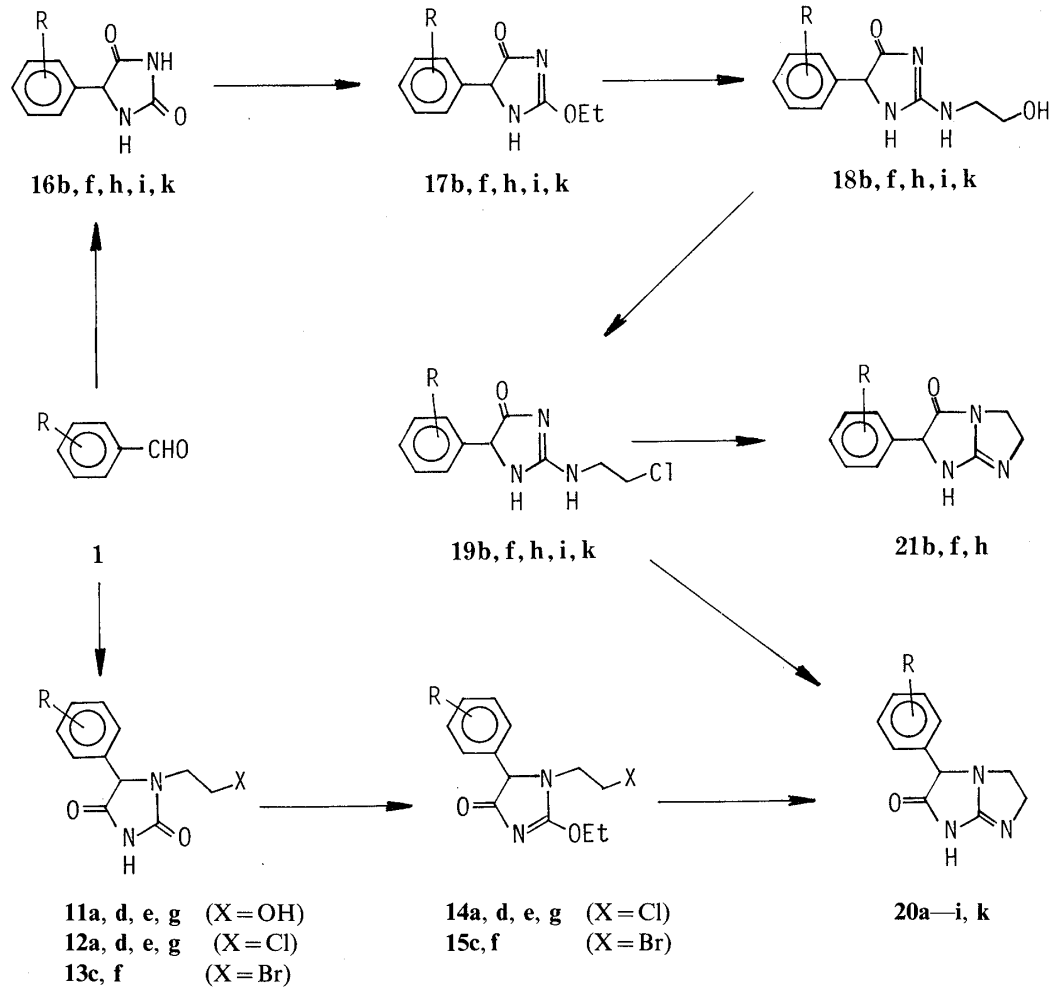


Chart 2

This signal was shifted downfield compared with that (δ 4.76) reported by Li *et al.*[6] because of the effect of the tautomeric C=N bond adjacent to the methine proton. These physicochemical properties of **10a** are different from those described by Li *et al.* or Van Gelder *et al.*

Preparation of 3-(substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-2-ones (**20**) was also carried out by two methods. Benzaldehydes (**1a**, **d**, **e**, **g**) were converted into 1-(2-hydroxyethyl)-5-(substituted phenyl)hydantoins (**11a**, **d**, **e**, **g**) in the presence of ethanolamine by the method described by Kawahara and Katsuno.[9] The compounds (**11**) were reacted with thionyl chloride to give the 1-(2-chloroethyl) derivatives (**12a**, **d**, **e**, **g**). In this reaction, the use of 2-bromoethylamine instead of ethanolamine directly gave 1-(2-bromoethyl) derivatives (**13c**, **f**) even if in poor yield. Treatment of **12** and **13** with the Meerwein reagent afforded the 2-ethoxy derivatives (**14a**, **d**, **e**, **g**) and (**15c**, **f**), respectively. Heating of **14** and **15** with ethanolic ammonia solution in a sealed tube gave the target compounds **20a**, **c**—**g**.

On the other hand, benzaldehydes (**1**) were converted to the corresponding 5-phenylhydantoin derivatives (**16b**, **f**, **h**, **i**, **k**) by the usual method. The compounds (**16**) were reacted with the Meerwein reagent to give the 2-ethoxy derivatives (**17b**, **f**, **h**, **i**, **k**). Heating of **17** with ethanolamine followed by chlorination afforded 2-(2-chloroethyl)imino-5-(substituted phenyl)hydantoins (**19b**, **f**, **h**, **i**, **k**) in good yields. It has been reported[10] that 5,5-diphenyl-2-(2-chloroethyl)iminohydantoin was converted into 3,3-diphenyl-2,3,5,6-tetrahydro-1*H*-imidazol[1,2-*a*]imidazol-2-one by treatment with base and into 2,2-diphenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-3-one by direct heating. As expected, **19b**, **f**, **h**, **i**, **k** ob-

tained here reacted with sodium hydride to give 3-(substituted phenyl)-2-one derivatives (**20b**, **f**, **h**, **i**, **k**), which were identical with those obtained from **14** or **15**.

Heating of **19b**, **f**, **h** at 180 °C also gave 2-(substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-3-one derivatives (**21b**, **f**, **h**). In these cyclizations of **19** to **20** or **21** the other isomer was not observed in the reaction mixture.

Biological Activities

2-(Substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles (**10**) obtained here and ICI-101187 were examined for antihypertensive and diuretic activities in spontaneously hypertensive rats (SHR), and the results are shown in Table I. The 2-chloro derivative (**10b**) was the most effective compound and its activity was equal to or greater than that of ICI-101187. The 2,4-dichloro (**10f**), 2,6-dichloro (**10h**), and 2,6-difluoro (**10j**) derivatives were potent antihypertensive agents. It appears that a halogen substituent at the 2- or 3-position of the phenyl ring is desirable for potent activity. An exception to this is the 2-chloro-6-fluoro derivative (**10i**). 4-Chloro substitution decreased the activity and introducing a methyl group into the phenyl ring yielded an inactive compound.

In the test of the antihypertensive effect in SHR, a potent diuretic activity was observed with **10h** and ICI-101187. Compounds **10** were also examined for diuretic activity in SHR. Among the compounds **10**, the most potent compound was the 2,6-dichloro derivative (**10h**), and the 2,6-dimethyl (**10l**). 2-Chloro-6-methyl (**10k**), and 2-chloro-6-fluoro (**10i**) compounds were also very active. Mono-substituted and 2,4- or 3,4-disubstituted compounds lacked the activity.

Generally the bicyclic guanidine derivatives have high acute toxicity. One possible way to decrease the toxicity might be to weaken the strong basicity of the guanidine moiety by introducing an oxo group into the imidazoline ring with the phenyl group. Some novel 3- or 2-(substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imazo[1,2-*a*]imidazol-2- (**20**) or -3-ones (**21**) were prepared and examined for antihypertensive and diuretic activity.

The antihypertensive activities of **20** and **21** were greatly diminished. On the other hand, the diuretic activity was almost wholly retained. The activity of **20** was more potent than that of **21**. Among the halo and methyl substituents in the phenyl group of **20**, a 4-chloro group increased the activity and a methyl group largely retained it.

Among the compounds showing potent diuretic activity in SHR, **10h**, **i**, **k** and **20d**, **f**, **k** were also examined in normotensive SLC-Wistar rats. The potencies of **10h**, **i**, **k** were almost equal to that of hydrochlorothiazide, as shown in Table I. However, **20d**, **f**, **k** were not effective.

This may suggest that contribution of the substituents of the phenyl group to the antihypertensive and diuretic activities are different from each other. Among the compounds **10**, **20** and **21**, **10h** seems to be the best compound. Evaluation of **10h** as a candidate for antihypertensive drug is in progress.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were taken on a Hitachi 285 spectrometer. ^{1}H-NMR spectra were recorded with Varian EM-360 (60 MHz), Hitachi R-40 (90 MHz), and XL-200 (200 MHz) spectrometers (Me_4Si as an internal standard, δ value). For column chromatography, Silica gel (Merck, 0.063—0.2 mm) was used.

α-Benzhydrylamino-2-chlorophenylacetonitrile (2b)——A solution of 2-chlorobenzaldehyde (**1b**) (43 g, 0.3 mol) in MeOH (200 ml) was added to a mixture of benzhydrylamine hydrochloride (67.5 g, 0.3 mol) and KCN (20 g, 0.3 mol) in H_2O (200 ml). The mixture was stirred at room temperature for 5 h and poured into H_2O (500 ml). The precipitate was extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated to dryness *in vacuo*, and the residue was recrystallized from benzene–petr.ether to give **2b** (85 g, 85%), mp 94—95 °C. IR (KBr): 3330, 2200, 1950 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.12 (1H, d, J=1.5 Hz), 4.84 (1H, d, J=12 Hz). *Anal.* Calcd for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42. Found: C, 75.98; H, 5.62; N, 8.80.

TABLE I. 2-(Substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles (**10**) and Their Biological Activities

Compd. No.	R	Yield Method	(%)	mp (°C) (recryst. solv.)	Analysis Formula Calcd (Found) C H N	IR (KBr) (cm^{-1})	^{1}H-NMR[a] (δ)	Biological activities[b] SHR[c] AA[e]	SHR[c] DA[f]	NR[d] DA[f]
10a	H	B	81	115—116 (AcOEt)	$C_{11}H_{13}N_3$ 70.56 7.00 22.44 (70.55 7.04 22.68)	1680	5.16 (t, J=7 Hz)	—[g]	—[h]	
10b	2-Cl	A B	55 69	133—134 (AcOEt)	$C_{11}H_{12}ClN_3$ 59.59 5.46 18.95 (59.64 5.45 19.16)	1670	5.58 (dd, J=6.5, 8 Hz)	+++	−	
10c[i]	3-Cl	B	58	186—189 (MeOH–Et_2O)	$C_{11}H_{12}ClN_3 \cdot HCl$ 51.18 5.07 16.26 (50.81 6.08 15.97)	1680	5.20 (t, J=8 Hz)[j]	++	++	
10d	4-Cl	B	52	140—142 (AcOEt)	$C_{11}H_{12}ClN_3$ 59.59 5.46 18.95 (59.34 5.59 18.82)	1680	5.15 (t, J=7 Hz)	−	+	
10e	4-Me	B	45	138—139 (AcOEt)	$C_{12}H_{15}N_3$ 71.61 7.51 20.88 (72.10 7.61 20.90)	1680	5.17 (t, J=8 Hz)	−	+	
10f	2-Cl, 4-Cl	A	53	150—151 (AcOEt)	$C_{11}H_{11}Cl_2N_3$ 51.58 4.33 16.41 (51.53 4.30 16.60)	1680	5.50 (dd, J=6.5, 8 Hz)	++	−	

10g	3-Cl, 4-Cl	B	66	117—119 (AcOEt)	$C_{11}H_{11}Cl_2N_3$ 51.58 4.33 16.41 (51.30 4.21 16.21)	1660	5.20 (t, J=8 Hz)	+	++	
10h	2-Cl, 6-Cl	A	43	165—166	$C_{11}H_{11}Cl_2N_3$	1670	6.13	++	+++	+++[h]
		B	57	(AcOEt)	51.58 4.33 16.41 (51.82 4.45 16.37)		(dd, J=8.5, 10 Hz)			
10i	2-Cl, 6-F	B	58	136—138 (AcOEt)	$C_{11}H_{11}ClFN_3$ 55.12 4.63 17.53 (55.35 4.72 17.79)	1670	5.84 (dd, J=7, 9 Hz)	±	±	+++
10j	2-F, 6-F	B	61	166—168 (AcOEt)	$C_{11}H_{11}F_2N_3$ 59.18 4.97 18.82 (59.17 5.02 18.42)	1670	5.62 (dd, J=7, 7.5 Hz)	+++	+	
10k	2-Cl, 6-Me	B	58	146—147 (AcOEt)	$C_{12}H_{14}ClN_3$ 61.15 5.99 17.83 (61.38 5.57 17.57)	1675	5.95 (dd, J=8, 10 Hz)	−	+++	+++
10l	2-Me, 6-Me	B	46	140—141 (AcOEt)	$C_{13}H_{17}N_3$ 72.52 7.96 19.52 (72.34 8.13 19.50)	1670	5.66 (dd, J=6.5, 7.5 Hz)	−	+++	
ICI-101187[k]								++	+++	
Hydrochlorothiazide[k]								−	+++	+++

a) Chemical shift of the methine proton at the 2-position of **10** in $CDCl_3$. *b*) Data are the means of five animals given the vehicle or a test compound at an oral dose of 50 mg/kg for the antihypertensive and 5 mg/kg for the diuretic activities (1—5 h after the dose). *c*) Spontaneous hypertensive rats. *d*) Normotensive SCL-Wistar rats. *e*) Antihypertensive activity. *f*) Diuretic activity. *g*) Decrease in systolic blood pressure: −, <10; ±, 10—20; +, 20—30; ++, 30—40; +++, >40 mmHg. *h*) Increase of urine volume: −, 0—10; +, 10—15; ++, 15—20; +++, >20 ml/kg. *i*) Data for the hydrochloride. *j*) Chemical shift in DMSO-d_6. *k*) These compounds were prepared in our Institute.

TABLE II. 3-(Substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-2-ones (**20**), 2-(Substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-2-one Hydrochlorides (**21**) and Their Biological Activities

Compd. No.	R	Method	Yield (%)	mp (°C) (recryst. solv.)	Analysis Formula Calcd (Found) C H N	IR (KBr) (cm^{-1})	^{1}H-NMR[a] (δ)	Biological activities[b] SHR AA	SHR DA	NR DA
20a	H	A	34	262—265 (dec.) (MeOH)	$C_{11}H_{11}N_3O$ 65.66 5.51 20.88 (65.56 5.71 20.58)	1735 1710	4.72	−	++	
20b	2-Cl	B	32	230—233 (EtOH)	$C_{11}H_{10}ClN_3O$ 56.06 4.28 17.83 (55.91 4.58 17.99)	1720 1600	5.51	+	+	
20c	3-Cl	A	11	225—228 (dec.) (EtOH)	$C_{11}H_{10}ClN_3O$ 56.06 4.28 17.83 (55.92 4.38 17.59)	1750 1680	4.76	±	++	
20d	4-Cl	A	11	241—245 (dec.) (MeOH)	$C_{11}H_{10}ClN_3O$ 56.06 4.28 17.83 (55.79 4.32 17.79)	1730 1625	4.77	±	+++	+
20e	4-Me	A	23	239—242 (dec.) (MeOH)	$C_{12}H_{13}N_3O$ 66.96 6.09 19.52 (66.88 6.19 19.36)	1720 1625	4.66	−	++	
20f	2-Cl, 4-Cl	A B	14 36	252—256 (dec.) (iso-PrOH)	$C_{11}H_9Cl_2N_3O$ 48.91 3.36 15.56 (49.06 3.76 15.95)	1720 1600	5.43	−	+++	−
20g	3-Cl, 4-Cl	A	7	253—255 (dec.) (MeOH)	$C_{11}H_9Cl_2N_3O$ 48.91 3.36 15.56 (48.87 3.59 15.64)	1720 1625	4.82	±	++	
20h	2-Cl, 6-Cl	B	22	240—243 (dec.) (*n*-BuOH)	$C_{11}H_9Cl_2N_3O$ 48.91 3.36 15.56 (48.99 3.40 15.58)	1730 1610	5.16	−	++	
20i	2-Cl, 6-F	B	35	232—235 (dec.) (*n*-BuOH)	$C_{11}H_9ClFN_3O$ 52.09 3.58 16.57 (52.21 3.67 16.30)	1720 1600	5.10	−	++	
20k	2-Cl, 6-Me	B	35	243—246 (dec.) (MeOH)	$C_{11}H_{11}ClN_3O$ 57.92 4.84 16.83 (57.97 5.19 16.73)	1720 1620	5.35	−	+++	+
21b	2-Cl		50	240—243 (dec.) (EtOH)	$C_{11}H_{10}ClN_3O \cdot HCl$ 48.56 4.07 15.44 (48.77 4.30 15.59)	1760 1720	6.15	−	+	
21f	2-Cl, 4-Cl		55	242—245 (dec.) (*n*-BuOH)	$C_{11}H_9Cl_2N_3O \cdot HCl$ 43.09 3.29 13.71 (42.89 3.30 13.62)	1770 1730	6.20	−	++	
21h	2-Cl, 6-Cl		55	270—273 (dec.) (EtOH)	$C_{11}H_9Cl_2N_3O \cdot HCl \cdot 0.5H_2O$ 41.86 3.51 13.32 (42.07 3.46 13.31)	1760 1720	6.54	±	+	

a) Chemical shifts (singlet) of the methine proton at the 3-position in **20** and at the 2-position in **21** in DMSO-d_6. *b*) See footnote in Table I.

Compounds **2f**, **h** were prepared in the same way as described above for **2b**.

2f: Yield, 90%, mp 112—114 °C (benzene–petr.ether). IR (KBr): 3300, 2200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.22 (1H, d, J=2 Hz), 4.86 (1H, d, J=11 Hz). *Anal.* Calcd for $C_{21}H_{16}Cl_2N_2$: C, 68.67; H, 4.39; N, 7.63. Found: C, 68.42; H, 4.35; N, 7.81.

2h: Yield, 94%, mp 137—139 °C (benzene–petr.ether). IR (KBr): 3300, 2200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.44 (1H, d, J=12 Hz), 5.21 (1H, s). *Anal.* Calcd for $C_{21}H_{16}Cl_2N_2$: C, 68.67; H, 4.39; N, 7.63. Found: C, 68.99; H, 4.45; N, 7.88.

2-Benzhydrylamino-2-(2-chlorophenyl)ethylamine (3b)——A solution of **2b** (73 g, 0.22 mol) in dry Et_2O (1.3 l) was added portionwise to a mixture of $LiAlH_4$ (25 g, 0.66 mmol) in dry Et_2O at 0—10 °C with stirring. The mixture was stirred at the same temperature for 5 h and then at room temperature overnight. After decomposition of excess $LiAlH_4$ in the usual manner, the organic layer was separated, dried and concentrated to dryness *in vacuo* to give **3b** (68 g, 92%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 4.65 (1H, s), 4.0—4.35 (1H, m), 2.7—3.15 (2H, m).

Compounds **3f, h** were prepared in a fashion analogous to that use for **3b** and these compounds **3b, f, h** were used for the next reaction without further purification.

3f: Yield 96%, oil. ^{1}H-NMR ($CDCl_3$) δ: 4.61 (1H, s), 3.9—4.2 (1H, m), 2.5—3.1 (2H, m).

3h: Yield 93%, oil. ^{1}H-NMR ($CDCl_3$) δ: 4.63 (1H, s), 3.7—4.15 (1H, m), 2.6—3.3 (2H, m).

1-Benzhydryl-5-(2-chlorophenyl)-2-cyanoiminoimidazolidine (4b)——A mixture of **3b** (10 g, 30 mmol) and dimethylcyanoimidodithiocarbonate (4.4 g, 30 mmol) was heated at 100—120 °C for 30 min and then at 190—210 °C for 30 min. The reaction residue was purified by silica gel (150 g) column chromatography with $CHCl_3$ as the eluent to give **4b** (5.5 g, 48%), mp 201—202 °C (acetone). IR (KBr): 2160, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.31 (1H, s), 5.43 (1H, dd, J=4, 10 Hz), 4.18 (1H, dd, J=9, 10 Hz), 3.31 (1H, dd, J=4, 9 Hz). *Anal.* Calcd for $C_{23}H_{19}ClN_4$: C, 71.40; H, 4.95; N, 14.48. Found: C, 71.42; H, 5.02; N, 14.56.

Compounds **4f, h** were also obtained as described above for **4b**.

4f: Yield 48%, mp 157—159 °C (*n*-hexane–Et_2O). IR (KBr): 2180, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.36 (1H, s), 5.37 (1H, dd, J=4, 10 Hz), 4.18 (1H, dd, J=10, 10 Hz), 3.26 (1H, dd, J=4, 10 Hz). *Anal.* Calcd for $C_{23}H_{18}Cl_2N_4$: C, 65.56; H, 4.31; N, 13.30. Found: C, 65.22; H, 4.42; N, 13.14.

4h: Yield 43%, mp 258—260 °C (acetone). IR (KBr): 2160, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.32 (1H, s), 6.08 (1H, dd, J=7.5, 11 Hz), 4.17 (1H, t, J=11 Hz), 3.57 (1H, dd, J=7.5, 11 Hz). *Anal.* Calcd for $C_{23}H_{18}Cl_2N_4$: C, 65.56; H, 4.31; N, 13.30. Found: C, 65.20; H, 4.41; N, 13.11.

1-Benzhydryl-3-(2-benzoyloxyethyl)-5-(2-chlorophenyl)-2-cyanoiminoimidazolidine (5b)——A mixture of **4b** (5 g, 13 mmol) and 50% NaH (0.62 g, 13 mmol) in dimethylformamide (DMF) (50 ml) was stirred at room temperature for 1 h, then 2-iodoethyl benzoate (3.6 g, 13 mmol) was added portionwise to the mixture with stirring. The mixture was stirred for 5 h, then poured into H_2O, and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated to dryness *in vacuo*. The residue was purified by silica gel (80 g) chromatography with $CHCl_3$ as the eluent to give **5b** (5.5 g, 80%), oil. IR (Neat): 2160, 1720, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.86 (1H, s), 5.32 (1H, dd, J=3, 10 Hz), 4.48 (1H, dd, J=9.5, 10 Hz), 3.75—4.7 (4H, m), 3.34 (1H, dd, J=3, 9.5 Hz).

Compound **5f, h** were prepared in a fashion analogous to that use for **5b**.

5f: Yield 51%, mp 140—141 °C (AcOEt). IR (KBr): 2170, 1725, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.77 (1H, s), 5.23 (1H, dd, J=3.5, 9.5 Hz), 4.3—4.8 (2H, m), 4.36 (1H, t, J=9.5 Hz), 3.8—4.2 (2H, m), 3.32 (1H, dd, J=3.5, 9.5 Hz). *Anal.* Calcd for $C_{32}H_{26}Cl_2N_4O_2$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.16; H, 4.57; N, 9.92.

5h: Yield 74%, oil. IR (Neat): 2160, 1715, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.74 (1H, s), 5.88 (1H, dd, J=6.5, 11 Hz), 4.45—4.8 (2H, m), 3.8—4.3 (2H, m), 4.37 (1H, dd, J=10, 11 Hz), 3.46 (1H, dd, J=6.5, 10 Hz).

2-(2-Aminoethyl)amino-1-(2-chlorophenyl)ethylalcohol (8b)——A mixture of ethylenediamine (90 g, 1.5 mol) and *o*-chlorostyrene oxide (**7b**) (15.5 g, 100 mmol) was heated at 60—70 °C with stirring and concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo* to give **8b** (18.7 g, 87%), mp 86—87 °C (Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 5.18 (1H, dd, J=4, 8.5 Hz), 2.3—3.05 (6H, m). *Anal.* Calcd for $C_{10}H_{15}ClN_2O$: C, 55.94; H, 7.04; N, 13.05. Found: C, 56.03; H, 7.00; N, 13.11.

Compounds **8a, d, h—l**, except for **8c**, mp 71—75 °C, **8e**, mp 101—103 °C, and **8g**, mp 73—75 °C, were oils, and were used for the next reaction without further purification.

1-(2-(2-Chlorophenyl)-2-hydroxyethyl)-2-iminoimidazolidine Hydrobromide (9b)——**8b** (14.4 g, 67 mmol) in benzene (300 ml) was added to a solution of BrCN (7.4 g, 70 mmol) in benzene (400 ml) with stirring. The mixture was stirred at room temperature for 3 h. The precipitate was collected and recrystallized from MeOH–Et_2O to give **9b** (17.5 g, 82%), mp 206—208 °C. IR (KBr): 3350, 1670, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.28 (1H, t, J=5 Hz) (free base). *Anal.* Calcd for $C_{11}H_{14}BrClN_3O$: C, 41.20; H, 4.72; N, 13.11. Found: C, 41.28; H, 4.77; N, 13.18.

Compounds **9a, c—e, g—l** were also obtained as described above for **9b**.

9a: Yield 78%, mp 181—182 °C (MeOH–Et_2O). IR (KBr): 3350, 1675, 1590 cm^{-1}. *Anal.* Calcd for $C_{11}H_{16}BrN_3O$: C, 46.16; H, 5.64; N, 14.68. Found: C, 46.16; H, 5.61; N, 14.71.

9c: Yield 35%, mp 176—179 °C (iso-PrOH). IR (KBr): 3330, 1680, 1600 cm^{-1}. *Anal.* Calcd for $C_{11}H_{15}BrClN_3O$: C, 41.20; H, 4.72; N, 13.11. Found: C, 41.35; H, 4.70; N, 13.14.

9d: Yield 59%, mp 182—183 °C (iso-PrOH). IR (KBr): 3300, 1670, 1500 cm^{-1}. *Anal.* Calcd for $C_{11}H_{15}BrClN_3O$: C, 41.20; H, 4.72; N, 13.11. Found: C, 41.25; H, 4.70; N, 13.09.

9e: Yield 61%, mp 192—196 °C (iso-PrOH). IR (KBr): 3300, 1680, 1600 cm^{-1}. *Anal.* Calcd for $C_{11}H_{18}BrN_3O$: C, 48.01; H, 5.71; N, 14.00. Found: C, 47.93; H, 5.71; N, 14.09.

9g: Yield 85%, mp 192—194 °C (iso-PrOH). IR (KBr): 3300, 1670, 1600 cm^{-1}. *Anal.* Calcd for $C_{11}H_{14}BrCl_2N_3O$: C, 37.21; H, 3.97; N, 11.83. Found: C, 37.20; H, 3.85; N, 11.84.

9h: Yield 92%, mp 212—214 °C (MeOH–Et_2O). IR (KBr): 3300, 1665, 1610 cm^{-1}. *Anal.* Calcd for $C_{11}H_{14}BrCl_2N_3O$: C, 37.21; H, 3.97; N, 11.83. Found: C, 37.10; H, 3.77; N, 11.67.

9i: Yield 53%, mp 207—209 °C (iso-PrOH). IR (KBr): 3300, 1670, 1605 cm^{-1}. *Anal.* Calcd for $C_{11}H_{14}BrClFN_3O$: C, 39.01; H, 4.17; N, 12.41. Found: C, 39.13; H, 4.25; N, 12.44.

9j: Yield 68%, mp 219—221 °C (MeOH–Et_2O). IR (KBr): 3340, 1675, 1625 cm^{-1}. *Anal.* Calcd for $C_{11}H_{14}BrF_2N_3O$: C, 41.01; H, 4.38; N, 13.04. Found: C, 41.03; H, 4.46; N, 12.96.

9k: Yield 68%, mp 201—202 °C (MeOH–Et_2O). IR (KBr): 3300, 1670, 1620 cm^{-1}. *Anal.* Calcd for $C_{12}H_{17}Cl_2N_3O$: C, 49.66; H, 5.91; N, 14.48. Found: C, 49.74; H, 5.79; N, 14.22.

9l: Yield 8%, mp 226—228 °C (MeOH–Et_2O). IR (KBr): 3300, 1660, 1580 cm^{-1}. *Anal.* Calcd for $C_{13}H_{20}ClN_3O$: C, 57.88; H, 7.47; N, 15.58. Found: C, 57.81; H, 7.28; N, 15.61.

2-(Substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (10)——Method A: A solution of **5b** (4.5 g, 10.5 mmol) in conc. HCl (70 ml) was refluxed for 6 h, then cooled, and washed with Et_2O. The water layer was concentrated *in vacuo*. The residue was mixed with $SOCl_2$ (40 ml) and the mixture was stirred at room temperature for 2 h. After evaporation of excess $SOCl_2$ *in vacuo*, the residue was mixed with KOH (6 g), H_2O (15 ml) and MeOH (45 ml) and refluxed for 5 h. Methanol was removed *in vacuo* and the residue was extracted with Et_2O. The extract was washed with H_2O, dried and concentrated to dryness *in vacuo* to give **10b** (1.2 g, 55%).

Compounds **10f, h** were also prepared by the same method as described above for **10b**. The results are shown in Table I.

Method B: **9a** (7.2 g, 25 mmol) was added to $SOCl_2$ (100 ml) with stirring, and the mixture was stirred at room temperature for 2 h. After removal of excess $SOCl_2$ *in vacuo*, the residue was worked up by a procedure similar to that described above to give the free base of **10a** (3.8 g, 81%), mp 115 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.26 (5H, m), 5.12 (1H, t, J=8 Hz, 2-H), 3.65 (2H, t like, J=8 Hz, 6-H), 3.49 (1H, t, J=8 Hz, 3-H), 3.12 (1H, m, 5-H), 2.92 (1H, m, 5-H), 2.67 (1H, t, J=8 Hz, 3-H). The free base was treated with HCl–MeOH solution to give the hydrochloride, mp 207—209 °C (dec.) (MeCN). *Anal.* Calcd for $C_{11}H_{14}ClN_3$: C, 59.09; H, 6.31; N, 18.78. Found: C, 59.10; H, 6.37; N, 19.11.

Compounds **10b—e, g—l** were also prepared as described above for **10a**. Since **10c** was obtained as an oil, the oily free base was converted to the hydrochloride in the usual way. The results are shown in Table I.

1-(2-Hydroxyethyl)-5-(substituted phenyl)imidazolidine-2,4-dione (11)——Compounds **11d, e, g** were obtained from the corresponding benzaldehydes (**1d, e, g**) by a method similar to that described by Kawahara and Katsuno[9] for the synthesis of the 5-phenyl derivative (**11a**).

11d: Yield 63%, mp 172—173 °C (MeOH). IR (KBr): 1765, 1745, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.25 (1H, s). *Anal.* Calcd for $C_{11}H_{11}ClN_2O_3$: C, 51.88; H, 4.35; N, 11.00. Found: C, 51.75; H, 4.13; N, 11.07.

11e: Yield 69%, mp 156—157 °C (MeOH). IR (KBr): 1765, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.11 (1H, s). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.35; H, 6.15; N, 11.76.

11g: Yield 66%, mp 154—156 °C (MeOH). IR (KBr): 1760, 1740, 1715 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.43 (1H, s). *Anal.* Calcd for $C_{11}H_{10}Cl_2N_2O_3$: C, 45.70; H, 3.49; N, 9.69. Found: C, 45.25; H, 3.48; N, 9.82.

1-(2-Chloroethyl)-5-(substituted phenyl)imidazolidine-2,4-dione (12)——Compounds **12d, e, g** were obtained from **11d, e, g**, respectively, by a method similar to that described by Zaugg *et al.*[11] for the synthesis of 5-phenyl derivative (**12a**).

12d: Yield 69%, mp 176—177 °C (acetone). IR (KBr): 1760, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.30 (1H, s). *Anal.* Calcd for $C_{11}H_{10}Cl_2N_2O_2$: C, 48.38; H, 3.69, N. 10.26. Found: C, 48.59; H, 3.72; N, 10.27.

12e: Yield 70%, mp 149—153 °C (acetone). IR (KBr): 1765, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.16 (1H, s). *Anal.* Calcd for $C_{12}H_{13}ClN_2O_2$: C, 57.04; H, 5.18; N, 11.09. Found: C, 57.40; H, 5.16; N, 11.18.

12g: Yield 89%, mp 171—172 °C ($CDCl_3$). IR (KBr): 1770, 1730 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.37 (1H, s). *Anal.* Calcd for $C_{11}H_9Cl_3N_2O_2$: C, 42.96; H, 2.95; N, 9.11. Found: C, 42.64; H, 2.90; N, 9.00.

1-(2-Bromoethyl)-5-(substituted phenyl)imidazolidine-2,4-dione (13)——Compounds **13c, f** were obtained from the corresponding benzaldehydes (**1c, f**) by a method similar to that described by Long *et al.*[12] for the synthesis of the 5-phenyl derivative (**13a**).

13c: Yield 13%, mp 110—111 °C (MeOH). IR (KBr): 1740, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.25 (1H, s). *Anal.* Calcd for $C_{11}H_{10}BrClN_2O_2$: C, 41.60; H, 3.17; N, 8.82. Found: C, 41.82; H, 3.20; N, 9.09.

13f: Yield 17%, mp 190—191 °C ($CDCl_3$). IR (KBr): 1760, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.60 (1H, s). *Anal.* Calcd for $C_{11}H_{10}BrCl_2N_2O_2$: C, 37.53; H, 2.58; N, 7.96. Found: C, 37.67; H, 2.73; N, 7.96.

1-(2-Chloroethyl)-2-ethoxy-5-(4-chlorophenyl)-2-imidazolin-4-one (14d)——A mixture of **13d** (1.0 g, 3.9 mmol) and the Meerwein reagent, prepared from $BF_3 \cdot Et_2O$ (1.7 g, 12 mmol) and epichlorohydrin (0.85 g, 9 mmol), in CH_2Cl_2 (20 ml) was stirred at room temperature overnight and poured into ice-cooled 10% Na_2CO_3 solution (35 ml). The organic layer was separated, washed with H_2O, dried, and concentrated to dryness *in vacuo*. The oily residue was purified by silica gel (30 g) chromatography using a mixture of $CHCl_3$–MeOH (20 : 1, v/v) as the eluent to give **14d** (0.73 g, 64%) as a crude oil. ^{1}H-NMR ($CDCl_3$) δ: 5.07 (1H, s).

Compounds **14a, e, g** were also prepared as described above for **14d**.

14a: Yield 52%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.10 (1H, s).

14e: Yield 72%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.04 (1H, s).

14g: Yield 53%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.11 (1H, s).

1-(2-Bromoethyl)-2-ethoxy-5-(3-chlorophenyl)-2-imidazolin-4-one (15c)——Compounds **15c, f** were prepared by a

method similar to that described above.

15c: Yield 38%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.04 (1H, s).

15f: Yield 14%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.54 (1H, s).

5-(Substituted phenyl)imidazolidine-2,4-dione (16)——Compounds **16b**, **h**, **i**, **k** were obtained from the corresponding benzaldehydes by a method similar to that described by Thornton and Marsh[13] for the synthesis of 5-phenylhydantoin (**16a**).

16b: Yield 39%, mp 165—169 °C (EtOH–H_2O). IR (KBr): 1780, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.50 (1H, s). *Anal.* Calcd for $C_9H_6ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.60; H, 3.50; N, 13.25.

16h: Yield 57%, mp 238—240 °C (MeOH). IR (KBr): 1780, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.95 (1H, s). *Anal.* Calcd for $C_9H_7Cl_2N_2O_2$: C, 44.11; H, 2.47; N, 11.43. Found: C, 44.10; H, 2.60; N, 11.45.

16i: Yield 48%, mp 217—220 °C (MeOH). IR (KBr): 1770, 1710 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.60 (1H, s). *Anal.* Calcd for $C_9H_6ClFN_2O_2$: C, 47.28; H, 2.65; N, 12.26. Found: C, 47.29; H, 2.73; N, 12.15.

16k: Yield 31%, mp 203—204 °C ($CDCl_3$–MeOH). IR (KBr): 1780, 1710 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.55, 5.70 (1H, s × 2), 2.20, 2.43 (3H, s × 2). *Anal.* Calcd for $C_{10}H_9ClN_2O_2$: C, 53.66; H, 4.04; N, 12.67. Found: C, 53.46; H, 3.98; N, 12.45.

5-(2-Chlorophenyl)-2-ethoxy-2-imidazolin-4-one (17b)——A mixture of **16b** (42.1 g, 200 mmol) and the Meerwein reagent [prepared from $BF_3 \cdot Et_2O$ (49 g, 250 mmol) and epichlorohydrin (24 g, 260 mmol)] in CH_2Cl_2 (800 ml) was refluxed with stirring for 6 h. The mixture was added to ice-cooled Na_2CO_3 solution. The organic layer was separated, washed with H_2O, dried, and concentrated to dryness to give **17b** (50.7 g, 80%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 5.55 (1H, s).

Compounds **17f**, **h**, **i**, **k** were prepared in a fashion analogous to that used to **17b**.

17f: Yield 94%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.45 (1H, s).

17h: Yield 85%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.90 (1H, s).

17i: Yield 66%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.50 (1H, s).

17k: Yield 87%, oil. ^{1}H-NMR ($CDCl_3$) δ: 5.4 (1H, br s).

5-(2-Chlorophenyl)-2-(2-hydroxyethyl)amino-2-imidazolin-4-one (18b)——A mixture of **17b** (46 g, 190 mmol) and aminoethanol (58.8 g, 950 mmol) in EtOH (600 ml) was refluxed with stirring for 2 h. The mixture was concentrated to a quarter of the initial volume *in vacuo* and the precipitate was collected by filtration to give **18b** (28.6 g, 58%), mp 218—221 °C. IR (KBr): 1700, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.22 (1H, s). *Anal.* Calcd for $C_{11}H_{12}ClN_3O_2$: C, 52.08; H, 4.77; N, 16.56. Found: C, 51.68; H, 4.94; N, 16.38.

Compounds **18f**, **h**, **i**, **k** were also obtained as described above for **18b**.

18f: Yield 58%, mp 200—203 °C. IR (KBr): 1690, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.23 (1H, s). *Anal.* Calcd for $C_{11}H_{11}Cl_2N_3O_2$: C, 45.85; H, 3.85; N, 14.58. Found: C, 45.73; H, 3.85; N, 14.98.

18h: Yield 52%, mp 212—214 °C. IR (KBr): 1690, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.53 (1H, s). *Anal.* Calcd for $C_{11}H_{11}Cl_2N_2O_2$: C, 45.85; H, 3.85; N, 14.58. Found: C, 45.81; H, 3.90; N, 14.80.

18i: Yield 26%, mp 190—194 °C. IR (KBr): 1690, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.2 (1H, s). *Anal.* Calcd for $C_{11}H_{11}ClFN_3O_2$: C, 48.63; H, 4.08; N, 15.47. Found: C, 48.64; H, 4.28; N, 15.11.

18k: Yield 58%, mp 220—225 °C. IR (KBr): 1720, 1630, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.15, 5.50 (1H, s × 2). *Anal.* Calcd for $C_{12}H_{14}ClN_3O_2$: C, 53.83; H, 5.27; N, 15.70. Found: C, 53.80; H, 5.36; N, 15.19.

2-(2-Chloroethyl)amino-5-(2-chlorophenyl)-2-imidazolin-4-one (19b)——Compound **18b** (27.9 g, 110 mmol) was added portionwise to ice-cooled $SOCl_2$ (150 ml) with stirring, then the mixture was stirred at room temperature for 5 h. After removal of excess $SOCl_2$ *in vacuo*, the residue was dissolved in MeOH (150 ml). The solution was added to $NaHCO_3$ solution and MeOH was evaporated off *in vacuo*. The precipitate was collected by filtration to give **19b** (26.3 g, 88%), mp 149—152 °C/235—240 °C (dec.). IR (KBr): 1705, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.22 (1H, s). *Anal.* Calcd for $C_{11}H_{11}Cl_2N_3O$: C, 48.55; H, 4.07; N, 15.44. Found: C, 48.28; H, 4.02; N, 16.68.

Compounds **19f**, **h**, **i**, **k** were also prepared in the manner above for **19b**.

19f: Yield 97%, mp 146—148 °C/237—240 °C (dec.). IR (KBr): 1700, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.25 (1H, s). *Anal.* Calcd for $C_{11}H_{10}Cl_3N_3O$: C, 43.09; H, 3.29; N, 13.71. Found: C, 43.00; H, 3.29; N, 13.81.

19h: Yield 93%, mp 156—157 °C/267—269 °C (dec.). IR (KBr): 1700, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.55 (1H, s). *Anal.* Calcd for $C_{11}H_{10}Cl_3N_3O$: C, 43.09; H, 3.29; N, 13.71. Found: C, 43.02; H, 3.29; N, 13.52.

19i: Yield 92%, mp 149—151 °C/241—248 °C (dec.). IR (KBr): 1690, 1640 cm^{-1}. *Anal.* Calcd for $C_{11}H_{10}Cl_2FN_3O$: C, 45.53; H, 3.47; N, 14.48. Found: C, 45.51; H, 3.49; N, 14.30.

19k: Yield 97%, mp 159—163 °C/258—261 °C (dec.). IR (KBr): 1700, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.53, 5.18 (1H, s × 2). *Anal.* Calcd for $C_{12}H_{13}Cl_2N_3O$: C, 50.36; H, 4.58; N, 14.69. Found: C, 50.18; H, 4.64; N, 14.52.

3-(Substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-2-one (20)——Method A: A solution of **15f** (1.05 g, 3.4 mmol) in 10% NH_3–EtOH (10 ml) was heated at 100 °C for 6 h in a sealed tube. The mixture was concentrated *in vacuo*. The residue was treated with dil. NaOH solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated to dryness *in vacuo*. This residue was purified by silica gel (15 g) chromatography with a mixture of $CHCl_3$–MeOH (10 : 1, v/v) to give **20f**.

Compounds **20a**, **c**—**e**, **g** were similarly prepared and the results are shown in Table II.

Method B: A mixture of **19f** (0.61 g, 2 mmol) and 50% NaH (100 mg, 2 mmol) was stirred at room temperature for 4 h and concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was recrystallized from iso-PrOH to give **20f**.

Compounds **20b**, **h**, **i**, **k** were prepared in a fashion analogous to that used for **20f** and the results are shown in Table II.

2-(Substituted phenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-3-one Hydrochloride (21)——Compound **19b** (0.54 g, 2 mmol) was heated at 180 °C for 30 min. The reaction residue was recrystallized from EtOH to give **21b**.

Compounds **21f**, **h** were also prepared as described above for **21b** and the results are shown in Table II.

Antihypertensive and Diuretic Activities in SHR——The biological experiments were performed in male or female SHR having a systolic blood pressure (SBP) of over 160 mmHg. All compounds were dissolved in water or suspended in 0.5% carboxymethyl cellulose (CMC) and administrated orally by gavage. The oral dosage volume was 7.5 ml/kg. The rats were pre-warmed at 55—60 °C for 3 min, and SBP was measured by the tail-cuff method prior to and at 1, 2, 3, and 5 h after the administration of a test compound. Urine was individually collected up to 5 h after the administration of a test compound.

Diuretic Activity in Normotensive Rats——Diuretic experiments were performed in male SLC-Wistar rats weighing 170—220 g, which had been fasted for 18 h and deprived of drinking water for 2 h before the test. All compounds were dissolved in water or suspended in 0.5% CMC and administrated orally by gavage. The oral dosage volume was 5 ml/kg, which was immediately followed by 25 ml/kg of saline load. Urine was individually collected up to 5 h after the administration of a test compound.

References and Notes

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